30. (Unchanged) The non-human animal of claim 28, which is a monkey.

REMARKS

Applicants have carefully studied the Final Office Action mailed on August 14, 2002, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Finality of the Office Action

In the Office Action, claims 2-16 have been finally rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 2-14 and 17-18 have been finally rejected under 35 U.S.C. § 103(a) as being obvious over the prior art.

Applicants respectfully note that, although the instant Office Action is deemed Final, all rejections presented in it are new. As specified at page 2 of the Office Action, all prior rejections (*i.e.*, indefiniteness rejections under 35 U.S.C. § 112, second paragraph, anticipation rejections under 35 U.S.C. § 102(b) and obviousness rejections under 35 U.S.C. § 103(a)) have been withdrawn in light of the applicants' amendments. In view of the fact that all outstanding rejections are being presented for the first time and for the reasons provided below, applicants respectfully traverse the finality of the present Office Action.

As specified in MPEP 706.07(a), "[u]nder present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)."

Although the section title at page 3 of the Office Action recites that the new rejections are necessitated by the applicants' amendments, the Examiner does not specify which amendments she refers to and does not explain how these amendments create new grounds for rejection that justify making the Office Action final. Applicants respectfully note that the new indefiniteness rejection involves the recitations "contacting" and "wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant", which recitations were present in claims 1 and 3 as filed. The new rejections under 35 U.S.C. § 103(a) address obviousness of the method to transduce stem cells using viral particles pseudotyped with RD114 and substantially free of producer cells and producer cell supernatant as well as cells produced by such method. This method and cells were recited in claims 1 and 17 and their dependent claims as filed. Thus, these rejections could and should properly have been made in the prior Office Action.

In summary, new rejections presented in the instant Office Action are neither necessitated by applicants' amendments of the claims nor based on information submitted in a recent information disclosure statement. Accordingly, in light of the current patent practice, these new rejections cannot be presented in a Final Office Action. Withdrawal of the finality of the Office Action is kindly requested.

Pending Claims

Claims 2-37 were pending and at issue in the application. Claims 19-37 have been withdrawn from examination as being drawn to a non-elected invention. Claims 2-16 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 2-14 and 17-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over the prior art.

As discussed below, claims 19-30, which contain all of the limitations of claim 17, have been improperly withdrawn from consideration. Accordingly, only claims 31-37 have been canceled as being drawn to a non-elected invention.

Claims 3 and 17 have been amended to more particularly point out and distinctly claim the invention. Support for the recitation "wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant" in claim 17, can be found, for example, in the original claims 1, 3 and 17 and at p. 15, ll. 8-15, p. 25, ll. 15-17 and Example 1 (in particular, at p. 35, l. 17 - p. 36, l. 33 and p. 40, ll. 11-22) of the specification. Specific support for the new recitation "whereby the transduced stem cells are capable of ... repopulating cell lineages when transplanted into a host" in claims 1 and 17 can be found, for example, in Example 1 (in particular, at p. 37, l. 13 - p. 39, l. 40 and p. 40, ll. 26-31) and Example 6 (p. 45). This feature was implicit to the claims as filed, so its addition does not narrow the claims. No new subject matter has been added as a result of the amendments, no new search is required, and no new issues are raised. Following entry of these amendments, claims 2-30 will be pending.

Restriction Requirement

In the Office Action, claims 19-37 have been withdrawn from examination as being drawn to a non-elected invention. Applicants respectfully traverse the finality of the Restriction Requirement with respect to claims 19-30 and request reconsideration of the Requirement to allow prosecution of claims 2-18 and 19-30 in the same application.

Specifically, the Examiner states that the inventions recited in claims 19 and 20 are patentably distinct from the inventions recited in claims 2-18 because they require additional method steps[1]. Applicants respectfully note that claims 19 and 20 are product claims that depend from claim 18, which in turn depends from claim 17. Claims 19 and 20 recite features of the cells of claims 17 and 18, and do not recite any additional "steps" for generation of such cells. Claim 18 calls for a population of stem cells transduced with retroviral vector particles containing a gene of interest, whereby the transduced stem cells are capable of expressing the gene of interest. Claims 19 and 20 specify the number of such cells expressing the gene of interest when transplanted and engrafted into a host. Claim 20 specifies that such cells have been transduced by a single exposure to the retroviral vector particles. As disclosed in Example 1 (in particular, p. 37, l. 13 - p. 39, l. 40 and p. 40, ll. 26-31) and Example 6 (p. 45) of the present specification, transduced stem cells of claims 17 and 18 possess the intrinsic property of being capable of engraftment, repopulating cell lineages, and expressing the gene of interest when transplanted into a host. To clarify this issue, claim 17 has been amended to explicitly recite the

[1] Because the claims are to products, not methods, this issue seems superfluous. Moreover, this statement misconstrues the law of dependent claims, which must further limit the claims from which they depend. The presence of additional limitations does not, somehow, create a new statutory class of invention for restriction purposes.

intrinsic feature "whereby the transduced stem cells are capable of ... repopulating cell lineages when transplanted into a host". It follows, that transplantation and engraftment do not represent separate method steps of claims 19 and 20 but are simply conditions for revealing intrinsic features of transduced stem cells of claims 17 and 18. Accordingly, claims 19 and 20 contain all limitations of claims 17 and 18 and should be considered together with these claims.

The Examiner further contends that claims 21-30 are drawn to different methods of using stem cells. This may well be the case, but applicants note that claims 21-30 all depend from claim 17 (*i.e.*, recite the use of the stem cells of claim 17). If claim 17 is patentable, these claims must be also patentable because all limitations of claim 17 are intrinsically present in these claims. In short, claims are not patentably distinct if they contain all of the limitations of the main claim. *See, e.g.*, 37 C.F.R. § 1.141(b). Moreover, the methods of claims 21-30 constitute a biotechnological process. 35 U.S.C. §103(b)(3). Consequently, any patent issuing on this application should contain claims for both the process of using as well as the composition of matter. 35 U.S.C. §103(b)(2).

In light of the foregoing arguments as well as the mandate of 35 U.S.C. §103(b), it is respectfully requested that claims 19-30 be examined together with claims 2-18 in the instant application.

35 U.S.C. § 112, Second Paragraph, Rejections

In the Action, claims 2-16 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner contends that the

recitations "contacting" and "wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant" make it unclear what steps are encompassed by the recited method. The Examiner further states that it is unclear whether the claims encompass the step of co-cultivation of producer cells and target cells.

Applicants respectfully traverse the rejection and note that the transduction method recited in the independent claim 3 consists of only one step, *i.e.*, contacting target cells with vector particles. All other limitations in claim 3 are included to specify the properties of the vector particles used for transduction, *i.e.*, that these vector particles (i) are pseudotyped with feline endogenous virus RD114 envelope protein, (ii) contain a gene of interest, and (iii) are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant. Applicants respectfully note that the Examiner has mischaracterized prior applicants' comments, because the limitation "substantially free of producer cells" clearly indicates that producer cells are not present during the transduction and therefore the step of co-cultivation of producer cells and target cells is not encompassed by the present claims.

In light of the foregoing, applicants respectfully submit that the rejection of the claims based upon 35 U.S.C. §112, second paragraph, is overcome and withdrawal of such is kindly requested.

35 U.S.C. §103(a) Rejections

In the Office Action, claims 2, 3, 8, 12-14, 17, and 18 stand rejected as being obvious over Onodera *et al.* (J. Virol., 1998, 72: 1769-1774) in view of Porter *et al.* (Hum. Gene Ther., 1996, 7: 913-919). The Examiner contends that Onodera teaches the efficient transduction of a B lymphoblastoid cell line with RD114 pseudotyped MPSV-based retroviral vector particles and suggests that these vector particles may be used for transduction of hematopietic stem cells. The Examiner further states that Porter teaches the efficient transduction of CD34+ bone marrow cells using RD114 pseudotyped vectors. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to transduce hematopoietic stem cells using retroviral particles pseudotyped with RD114 and substantially free of producer cells or producer cell supernatant.

Applicants respectfully traverse the rejection and submit that, even if taken together, the cited references do not disclose or suggest the methods and products recited in the present claims and necessarily fail to provide a reasonable expectation of achieving the invention.

The courts have held that where the prior art seeks to solve the same problem as the claimed invention but lacks significant elements of the claimed invention, it is improper to view the invention in a piecewise fashion to find its elements in the prior art. On the contrary, the invention must be viewed as a whole. *Gore*, 721 F.2d 1540 (Fed. Cir. 1983); and *Phillips*, 673 F. Supp. 1278 (D. Del. 1987). Even where the elements of the claimed invention are known, the claimed invention may still be patentable. *Gillette*, 919 F.2d at 725. Further, it is improper to use hindsight to combine elements found in the prior art to reconstruct the claimed invention.

Gore, 721 F.2d at 1552. In considering obviousness, the critical inquiry is whether something in the prior art as a whole suggests the desirability, and thus the obviousness, of making a combination. *In re Newell*, 891, F.2d 899, 901-02, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir.1992). The Examiner must show some objective teaching from the art that would lead an individual to combine the references, *i.e.*, there must be motivation. In particular, the mere fact that the teaching of a reference may be modified in some way so as to achieve the claimed invention does not render the claimed invention obvious unless the prior art suggested the desirability of the modification (emphasis added). *In re Fritch*, 972 F.2d 1260, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir.1992) and see also *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (Bd. Pat. App. & Intf. 1993). In other words, determination that the invention is obvious requires that (i) cited references teach the claimed invention as a whole, and (ii) both the suggestion of making the invention, and a reasonable expectation of success can be found in the prior art, not in the applicants' disclosure. MPEP Section 2143; *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that neither of these criteria has been met. None of the references cited in the instant Office Action provides a suggestion to be combined with the other references or to modify the disclosed method of transduction, so that it becomes in any way analogous to the method recited in the present claims.

Claims 2, 3, 8, 12-14, 17, and 18 call for a method for transducing stem cells with vector particles (and the resulting transduced stem cells), wherein the vector particles are substantially free of both producer cells and producer cell supernatant. In contrast, as acknowledged by the Examiner at page 4 of the Office Action, Onodera teaches only

transduction using viral particles which are free of the producer cells but are not free of the producer cell supernatant (*see, e.g.*, section entitled "Transduction protocol" in the right col. at p. 1770 of the article). Since the supernatant contains the viral particles in Onodera, it must be present to achieve infection. Any suggestion to the contrary requires importing features simply not found in this reference. As further acknowledged by the Examiner at page 5 of the Office Action, Porter teaches transduction by co-cultivation of target cells with producer cells, *i.e.*, transduction using viral particles which are neither free of the producer cells nor free of the producer cell supernatant. In fact, Porter teaches away[2] from the present invention by disclosing that co-cultivation of target cells with producer cells is a superior method because it maximizes the efficiency of infection (*see, e.g.*, p. 915, left col., ¶3 and right col., ¶ 2, and Table 3 at p. 917). The present invention establishes that such co-cultivation is both unnecessary and undesirable.

As recited in the present claims, the RD114 pseudotyped vector particles of the invention are substantially free of factors that induce stem cell differentiation. This property of the vector particles constitutes an important advantageous feature of the instant invention. Specifically, as disclosed at p. 25, ll. 15-17 and Example 1 (*see, e. g.*, p. 35, l. 17 - p. 36, l. 33 and p. 40, ll. 11-22) of the specification, producer cells generating the RD114 pseudotyped vector particles (and therefore producer cell supernatant) may contain a substance that, upon transduction, induces highly undesirable differentiation and depletion of repopulating stem cells. As further disclosed in the application (*see, e.g.*, p. 15, ll. 8-15) and recited in the present claims, the vector particles of the invention become substantially free of factors that induce stem cell

[2] Where prior art references teach away from the claimed invention, it has been held that the claimed invention is nonobvious. *W.L. Gore & Associates., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551-2 (Fed. Cir. 1983).

differentiation, *e.g.*, by being substantially free of producer cells and producer cell supernatant. In contrast to the present invention, neither Onodera nor Porter disclose or suggest that the vector particles should be free of factors that induce stem cell differentiation. In fact, both references are completely silent with respect to transduction-induced stem cell differentiation and its harmful effect on stem cells' ability to repopulate cell lineages when transplanted into a host.

Furthermore, as disclosed in Examples 1 and 6 of the specification and recited in the claims as amended, the transduced stem cells of the instant invention are capable of repopulating cell lineages (*e.g.*, myeloid and lymphoid) when transplanted into a host (*e.g.*, immunodeficient mice or monkey). Neither Onodera nor Porter disclose that, upon transduction with RD114 pseudotyped viral particles, stem calls can be efficiently engrafted into a host to repopulate cell lineages. In fact, as admitted by the Examiner at p. 4 of the Office Action, Onodera does not even disclose but merely suggests that transduction of stem cells with RD114 pseudotyped viral particles can be achieved. This mere suggestion cannot provide a requisite expectation of success.

It follows that, even if taken together, the Onodera and Porter references do not disclose or suggest the methods and products recited by the present claims, much less provide a reasonable expectation of successfully achieving the claimed invention. Furthermore, because all of the obviousness rejections presented in the instant Office Action are based on the erroneous conclusion that Onodera and Porter, in combination, suggest or teach contacting target cells with producer cell-free and producer cell supernatant-free viral particles, all of the remaining rejections necessarily fall. The detailed discussion of these remaining rejections is provided below.

In the Office Action, claims 4-6 stand rejected as being obvious over Onodera in view of Porter, and further in view of Moritz *et al.* (Blood, 1996, 3:855-862) and Hanenberg *et al.* (Nature Medicine, 1996, 2: 876-882). The Examiner contends that Moritz supplements the disclosure of the primary references by teaching that binding to fibronectin improves the transduction efficiency of the retroviral vectors and that such improvement is due to direct binding of retroviral particles to carboxy-terminal fibronectin fragment FN30/35. The Examiner further states that Hanenberg teaches that binding of retroviral particles to retronectin (fibronectin fragment CH-296) results in a very efficient transduction of both human and murine hematopoietic cells. The Examiner concludes that the skilled artisan would have been motivated to combine the teachings of Onodera and Porter with the teachings of Moritz and Hanenberg to develop a method to improve the transduction efficiency of stem cells with RD114 pseudotyped viral vectors by using an adherence-promoting agent such as retronectin.

Applicants respectfully traverse the rejection and note that claims 4-6 call for a method for transducing stem cells using retroviral vector particles which (i) are pseudotyped with feline endogenous virus RD114 envelope protein, (ii) are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant, and (iii) are pre-adsorbed onto a surface that promotes adherence of the retroviral particles. As specified above and acknowledged by the Examiner at p. 6 of the Office Action, neither Onodera nor Porter disclose or suggest that the vector particles should be substantially free of both producer cells and producer cell supernatant or should be pre-adsorbed onto a surface that promotes adherence of the retroviral particles. As specified in the applicants' response to the previous Office Action, the present application discloses that several adhesion

promoting agents are useful for the transduction method of the invention, *e.g.*, polylysine and various derivatives of fibronectin including retronectin (fibronectin fragment CH-296) (*see, e.g.*, p. 27, ll. 3-4). Moritz provides no motivation to use retronectin or any other adhesion promoting agent except for fibronectin fragment FN 30/35 (different from retronectin), which it claims to be superior for efficient transduction (*see, e.g.*, p. 860, left col., ¶2). Furthermore, neither Moritz nor Hanenberg disclose or suggest the use of RD114 pseudotyped retroviral particles. These references focus on experiments using either producer cell supernatant or co-cultivation of target cells with producer cells (*see, e.g.*, Moritz: p. 856, right col.; Hanenberg: p. 877, right col., p. 878, right col., p. 880, left col., and Figure 7). Taken for what they fairly teach, the combined references provide for contacting stem cells with an RD114 pseudotyped retrovirus producer cells or producer cell supernatant. Given the explicit, inflexible teaching of the primary references for the presence of producer cells and/or producer cell supernatant for infection with RD114 pseudotyped viral particles, there is a strong disincentive to contact stem cells with viral particles free of <u>both</u> producer cells and producer cell supernatant. Thus, in contrast to the present invention, none of the cited references recognize that, to attain an efficient transduction and obtain stem cells capable of repopulating cell lineages in a host, retroviral particles have to be substantially free of factors that induce stem cell differentiation, *i.e.*, substantially free of producer cells and producer cell supernatant.

In summary, none of the cited references provide a reasonable expectation of success much less a suggestion of the transduction method recited in claims 4-6. The actual teachings of the references taken as a whole do not suggest the claimed invention, and the rejection requires impermissible hindsight reconstruction of various unconnected bits and pieces

of the references to sustain itself. It is well settled however, that such hindsight reconstruction is an error. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *Fritch*, 23 U.S.P.Q.2d at 1784. The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]". *Dow Chemical Co.*, 5 U.S.P.Q.2d at 1532.

In the Office Action, the Examiner has also rejected claims 10 and 11 as being unpatentable over Onodera in view of Porter, and further in view of Moritz, based on the assertion that Moritz teaches that the target cells are pre-stimulated with IL-6, rhSCF and polybrene prior to retroviral infection.

Applicants respectfully traverse the rejection, because, for the reasons presented above, the combination of Onodera and Porter fails to teach or suggest the claimed invention. Moritz, as set forth above, does not supply the missing teaching. Applicants respectfully submit that claims 10 and 11 call for a method for transducing stem cells using retroviral vector particles which (i) are pseudotyped with feline endogenous virus RD114 envelope protein, (ii) are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant, and (iii) are pre-stimulated. Neither Onodera nor Porter disclose or suggest that the vector particles should be substantially free of both producer cells and producer cell supernatant or should be pre-stimulated. Applicants note that Moritz does not provide any motivation to be combined with either Onodera or Porter and does not cure the

deficiency of the primary references, because, in contrast to the present invention, it does not recognize that, to attain an efficient transduction and obtain stem cells capable of repopulating cell lineages in a host, retroviral particles have to be substantially free of factors that induce stem cell differentiation, *i.e.*, substantially free of producer cells and producer cell supernatant. Moritz also does not disclose or suggest the use of RD114 pseudotyped retroviral particles. It follows then, that none of the cited references, even if artificially combined, suggest the claimed invention, much less provide a reasonable expectation of success of transducing cells as recited in claims 10 and 11.

Claim 7 stands rejected as being obvious over Onodera in view of Porter, and further in view of Rebel (Blood, 1999, 93: 2217-2224). The Examiner contends that Rebel supplements teachings of the primary references by disclosing the use of ultracentrifugation to remove producer cells and producer cell supernatant and attain high titers of viral particles during transduction.

Applicants respectfully traverse the rejection and note that claim 7 calls for a method for transducing stem cells using retroviral vector particles which (i) are pseudotyped with feline endogenous virus RD114 envelope protein and (ii) are freed of producer cells and producer cell supernatant by ultracentrifugation. As specified above, neither Onodera nor Porter disclose or suggest that the vector particles should be freed of producer cells and producer cell supernatant. On the contrary, they require one or the other component. Rebel does not disclose or suggest the use of RD114 pseudotyped retroviral particles. In fact, Rebel teaches away from using RD114 pseudotyped retroviral particles of the primary references by stressing the superior properties of VSV-G pseudotyped viral particles (*see, e.g.*, p. 2217, left col. and p. 2222,

concluding ¶). The requirement to include supernatant and/or producer cells for RD114 pseudotyped vectors set forth in Onodera and Porter precludes combining these references with Rebel, absent selective hindsight gained from the application.

In summary, none of the cited references provides a suggestion or motivation to be combined with the other references and, even if taken together, these references do not disclose or suggest the transduction method recited in claim 7.

In the Action, claim 9 stands rejected as being obvious over Onodera in view of Porter, and further in view of Uchida *et al.* (Proc. Natl. Acad. Sci. USA, 1998, 95: 11939-11944). The Examiner contends that Uchida supplements the disclosure of the primary references by teaching lentiviral vector-mediated gene transfer into hematopoietic stem cells.

Applicants respectfully traverse the rejection and note that claim 9 calls for a method for transducing stem cells with lentiviral vector particles, which (i) are pseudotyped with feline endogenous virus RD114 envelope protein and (ii) are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant. As acknowledged by the Examiner at p. 9 of the Office Action, neither Onodera nor Porter teach or suggest the use of lentiviral vectors. Uchida does not supply the missing teaching, because it does not disclose or suggest the use of RD114 protein to pseudotype the lentiviral particles. In fact, this article teaches away from the use of RD114-pseudotyped particles of the primary references by describing superior stem cell transduction properties of VSV-G pseudotyped lentiviral particles. As specified in Example 5 of the instant application, the present inventors were the first to create the RD114-pseudotyped lentiviral particles in the process that required a significant and non-routine experimentation. Furthermore, none of the

cited references (including Uchida) provide a suggestion or motivation to contact the stem cells with viral particles which are both producer cell-free and producer cell supernatant-free.

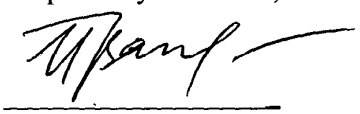
In summary, none of the cited references provide a suggestion to be combined with the other references, and, even if taken together, do not disclose or suggest the transduction method recited in claim 9.

In light of the foregoing arguments, it is respectfully submitted that pending claims are not obvious over the cited art. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2-30 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,



Date: February 13, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Patrick F. Kelly; Elio F. Vanin

Serial No.: 09/801,302 Art Unit: 1636

Filed: March 7, 2001 Examiner: Celine X. Qian

Confirmation No.: 2679

For: HIGHLY EFFICIENT GENE TRANSFER INTO HUMAN REPOPULATION STEM CELLS BY RD114 PSEUDOTYPED RETROVIRAL VECTOR PARTICLES

MARK-UP FOR AMENDMENT OF FEBRUARY 13, 2003

Pursuant to 37 C.F.R. §1.121, applicants provide the following mark-up copy of the amendments requested for the claims in the above-referenced application. This document is submitted simultaneously with an Amendment and Response to the Final Office Action mailed on August 14, 2002.

AMENDMENT

CLAIMS:

2. (Unchanged) The method of claim 3, wherein the vector particle is a retroviral vector particle comprising a modified retroviral genome containing the gene of interest.

3. (Amended) A method for transducing stem cells with a vector particle containing a gene of interest, which method comprises contacting target stem cells with vector particles pseudotyped with feline endogenous virus RD114 envelope protein and containing a gene of interest, wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant, and whereby the transduced stem cells are capable of expressing the gene of interest and repopulating cell lineages when transplanted into a host.

4. (Unchanged) The method of claim 2, wherein the retroviral particles are pre-adsorbed onto a surface that promotes adherence of the retroviral particles.

5. (Unchanged) The method of claim 4, wherein the surface is coated with an adherence promoting agent.

6. (Unchanged) The method of claim 5, wherein the adherence promoting agent is retronectin.

7. (Unchanged) The method of claim 2, wherein the retroviral particles are freed of producer cells and producer cell supernatant by ultracentrifugation.

8. (Unchanged) The method of claim 2, wherein the retroviral particle is an oncoviral particle.

9. (Unchanged) The method of claim 2 wherein the retroviral particle is a lentiviral particle.

10. (Unchanged) The method of claim 3 wherein the target stem cells are pre-stimulated.

11. (Unchanged) The method of claim 10, wherein the target stem cells are prestimulated by treatment with signaling molecules selected from the group consisting of cytokines, growth factors and phytohemagglutinin.

12. (Unchanged) The method of claim 3 wherein the target stem cells are hematopoietic stem cells.

13. (Unchanged) The method of claim 12 wherein the target hematopoietic stem cells are selected from the group consisting of cord blood cells, mobilized peripheral blood cells, bone marrow cells, and liver.

14. (Unchanged) The method of claim 13, wherein the target hematopoietic stem cells are selected from the group consisting of CD34+ cells and CD34+ CD38- cells.

15. (Unchanged) The method according to claim 2, wherein upon engraftment of the transduced stem cells contacted one time with the retroviral particles into a host, greater than 10% of the transduced cells express the gene of interest.

16. (Unchanged) The method according to claim 15, wherein greater than about 40% of the transduced cells express the gene of interest.

17. (Amended) A population of stem cells transduced with vector particles pseudotyped with feline endogenous virus RD114 envelope protein and containing a gene of interest, wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant and whereby the transduced stem cells are capable of expressing the gene of interest and repopulating cell lineages when transplanted into a host.

18. (Unchanged) The population of stem cells of claim 17, wherein the vector particle is a retroviral particle comprising a modified retroviral genome containing the gene of interest.

19. (Unchanged) The population of stem cells of claim 18, wherein upon engraftment of the stem cells into a host, the number of stem cells in the host that express the gene of interest is greater than 10% times a number of exposures of the stem cells to the retroviral vector particles.

20. (Unchanged) The population of stem cells of claim 18, wherein the stem cells were transduced by a single exposure to the retroviral vector particles and upon engraftment of the stem cells into a host, greater than about 40% of the stem cells express the gene of interest.

21. (Unchanged) A method for introducing a gene of interest into a host, which method comprises introducing the transduced stem cells of claim 17 into a host.

22. (Unchanged) The method according to claim 21, wherein the host is a human and the stem cells are human stem cells.

23. (Unchanged) The method according to claim 21, wherein the host is an immunodeficient animal and the stem cells are human stem cells.

24. (Unchanged) The method according to claim 21, wherein upon engraftment of the transduced stem cells contacted one time with the retroviral particles into a host, greater than 10% of the transduced cells express the gene of interest.

25. (Unchanged) The method according to claim 24, wherein greater than about 40% of the transduced stem cells express the gene of interest.

26. (Unchanged) A method of treating a disease or disorder, which method comprises administering to a patient a therapeutically effective dose of the transduced stem cells of claim 17, wherein the gene of interest is a therapeutic gene.

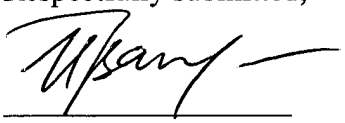
27. (Unchanged) The method of claim 26, wherein the disease or disorder is selected from the group consisting of hematopoietic disease, neural disease, joint-related disease, muscular disease, and liver disease.

28. (Unchanged) A non-human animal engrafted with the stem cells of claim 17.

29. (Unchanged) The non-human animal of claim 28, which is an immunodeficient mouse.

30. (Unchanged) The non-human animal of claim 28, which is a monkey.

Respectfully submitted,



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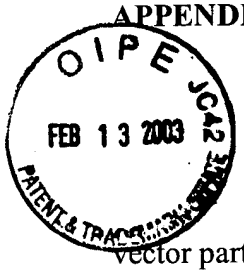

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2. (Unchanged) The method of claim 3, wherein the vector particle is a retroviral vector particle comprising a modified retroviral genome containing the gene of interest.

3. (Amended) A method for transducing stem cells with a vector particle containing a gene of interest, which method comprises contacting target stem cells with vector particles pseudotyped with feline endogenous virus RD114 envelope protein and containing a gene of interest, wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant, and whereby the transduced stem cells are capable of expressing the gene of interest and repopulating cell lineages when transplanted into a host.

4. (Unchanged) The method of claim 2, wherein the retroviral particles are pre-adsorbed onto a surface that promotes adherence of the retroviral particles.

5. (Unchanged) The method of claim 4, wherein the surface is coated with an adherence promoting agent.

6. (Unchanged) The method of claim 5, wherein the adherence promoting agent is retronectin.

7. (Unchanged) The method of claim 2, wherein the retroviral particles are freed of producer cells and producer cell supernatant by ultracentrifugation.

8. (Unchanged) The method of claim 2, wherein the retroviral particle is an oncoviral particle.

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9. (Unchanged) The method of claim 2 wherein the retroviral particle is a lentiviral particle.

10. (Unchanged) The method of claim 3 wherein the target stem cells are pre-stimulated.

11. (Unchanged) The method of claim 10, wherein the target stem cells are prestimulated by treatment with signaling molecules selected from the group consisting of cytokines, growth factors and phytohemagglutinin.

12. (Unchanged) The method of claim 3 wherein the target stem cells are hematopoietic stem cells.

13. (Unchanged) The method of claim 12 wherein the target hematopoietic stem cells are selected from the group consisting of cord blood cells, mobilized peripheral blood cells, bone marrow cells, and liver.

14. (Unchanged) The method of claim 13, wherein the target hematopoietic stem cells are selected from the group consisting of CD34+ cells and CD34+ CD38- cells.

15. (Unchanged) The method according to claim 2, wherein upon engraftment of the transduced stem cells contacted one time with the retroviral particles into a host, greater than 10% of the transduced cells express the gene of interest.

16. (Unchanged) The method according to claim 15, wherein greater than about 40% of the transduced cells express the gene of interest.

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17. (Amended) A population of stem cells transduced with vector particles pseudotyped with feline endogenous virus RD114 envelope protein and containing a gene of interest, wherein the vector particles are substantially free of factors that induce stem cell differentiation by being substantially free of producer cells and producer cell supernatant and whereby the transduced stem cells are capable of expressing the gene of interest and repopulating cell lineages when transplanted into a host.

18. (Unchanged) The population of stem cells of claim 17, wherein the vector particle is a retroviral particle comprising a modified retroviral genome containing the gene of interest.

19. (Unchanged) The population of stem cells of claim 18, wherein upon engraftment of the stem cells into a host, the number of stem cells in the host that express the gene of interest is greater than 10% times a number of exposures of the stem cells to the retroviral vector particles.

20. (Unchanged) The population of stem cells of claim 18, wherein the stem cells were transduced by a single exposure to the retroviral vector particles and upon engraftment of the stem cells into a host, greater than about 40% of the stem cells express the gene of interest.

21. (Unchanged) A method for introducing a gene of interest into a host, which method comprises introducing the transduced stem cells of claim 17 into a host.

22. (Unchanged) The method according to claim 21, wherein the host is a human and the stem cells are human stem cells.

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23. (Unchanged) The method according to claim 21, wherein the host is an immunodeficient animal and the stem cells are human stem cells.

24. (Unchanged) The method according to claim 21, wherein upon engraftment of the transduced stem cells contacted one time with the retroviral particles into a host, greater than 10% of the transduced cells express the gene of interest.

25. (Unchanged) The method according to claim 24, wherein greater than about 40% of the transduced stem cells express the gene of interest.

26. (Unchanged) A method of treating a disease or disorder, which method comprises administering to a patient a therapeutically effective dose of the transduced stem cells of claim 17, wherein the gene of interest is a therapeutic gene.

27. (Unchanged) The method of claim 26, wherein the disease or disorder is selected from the group consisting of hematopoietic disease, neural disease, joint-related disease, muscular disease, and liver disease.

28. (Unchanged) A non-human animal engrafted with the stem cells of claim 17.

29. (Unchanged) The non-human animal of claim 28, which is an immunodeficient mouse.

30. (Unchanged) The non-human animal of claim 28, which is a monkey.